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Validated Smoking Cessation and Prognosis in Patients With Stable Coronary Heart Disease

To the Editor: Patients with cardiovascular disease (CVD) should experience particularly substantial benefits from smoking cessation. A pertinent meta-analysis estimated that the relative odds of death in quitting compared with continuing smokers after myocardial infarction were 0.54 (95% confidence interval: 0.46 to 0.62) (1).

However, most published studies have relied only on self-report to estimate the impact of smoking cessation on the prognosis of patients with coronary heart disease (1). Relying on self-report alone leads to a substantial underestimation of the protective effects of smoking cessation (2). Therefore, we present updated analyses of the prospective KAROLA (Langzeiterfolge der Kardiologischen Anschlussheilbehandlung [Long-Term Success of Cardiologic Rehabilitation Therapy]) cohort study (2). Patients admitted from January 1999 to May 2000 to 1 of 2 participating rehabilitation clinics for in-hospital rehabilitation within 3 months after acute myocardial infarction or coronary syndrome or coronary artery intervention were eligible for participation, conditional on the provision of written informed consent. The study was approved by the ethics boards of the physicians' chambers of Hessen and Baden-Württemberg and of the University of Ulm and the University of Heidelberg.

Baseline and follow-up procedures featuring self-administered standardized questionnaires for patients and treating physicians over 8 years have been described elsewhere (2). Causes of death were ascertained through public health authorities. Blood samples for smoking status validation were taken at rehabilitation discharge and 1 and 3 years later by the participants' general practitioners. The samples were mailed to the study center and stored at −80°C until analysis, for which a commercial serum cotinine radioimmunoassay was used (Immundiagnostik AG, Bensheim, Germany).

Smoking behavior was handled in 4 different ways. First, participants were classified as nonsmokers (<15 ng/ml) or smokers (≥15 ng/ml) on the basis of cotinine levels at the end of the inpatient rehabilitation program (3). Second, the nonsmokers were further differentiated according to self-report (obtained through questionnaires at the beginning of inpatient rehabilitation) into never smokers, former smokers, and former smokers who had quit only after their acute cardiovascular events. Third, analyses were restricted to participants whose cotinine-based status did not change from baseline to years 1 and 3 follow-up (although this introduced a positive bias by including follow-up information as if available at baseline, it represented an informative extreme exposure comparison). Last, all cotinine information was ignored, and self-report was relied on solely.

The main analysis was by Cox models predicting secondary cardiovascular events (physician-reported nonfatal myocardial infarction or ischemic stroke or CVD as main cause of death [International Classification of Diseases-9th Revision, codes 390 to 459; International Classification of Diseases-10th Revision, codes I00 to I99; 1 case of code R57.0]). Adjusted models controlled for confounders important in our cohort (2).

Of 1,206 subjects initially included, complete data were available for 1,062 (88.1%). The participants were predominantly men (84.7%), with a mean age of 59 ± 8.0 years. The median observation time was 8.1 years (interquartile range: 6.1 to 8.2 years), and 154 secondary CVD events occurred. Of these, 51 were nonfatal myocardial infarctions, 41 were nonfatal ischemic strokes, and 62 were deaths with CVD as the main cause.

Cotinine measurements revealed nonabstinence at rehabilitation discharge in 123 of 1,009 participants (12.2%) who, according to self-report, were abstinent at the start of inpatient rehabilitation. At the same time, 22 of 53 participants (41.5%) who reported continuing to smoke at the beginning of rehabilitation had discharge cotinine values less than 15 ng/ml, suggesting that they had since quit. For 948 and 833 subjects, serum cotinine concentrations were also available for year 1 and 3 follow-up, respectively. On the basis of these measurements, 159 of 908 participants (17.5%) who were abstinent at baseline started or restarted smoking during follow-up (cotinine at years 1 or 3 ≥15 ng/ml), whereas 56 of 154 participants (36.4%) who had continued smoking at the end of inpatient rehabilitation quit smoking at least temporarily during this time (cotinine at years 1 or 3 <15 ng/ml).

Compared with continuing smokers, risks were reduced for all other groups, regardless of how smoking status was assessed (Table 1). The risk in participants classified as abstinent on the basis of cotinine measurements was halved. With additional differentiation on the basis of self-report, the risk was estimated to be reduced by more than 50% in both never smokers and those who had quit after their acute CVD events. If misclassification was further reduced by excluding participants whose smoking status changed during follow-up, subjects in all 3 nonsmoking categories showed strongly reduced risk in comparison with continuing smokers, with reductions of about 70% and 80%. In contrast, when cotinine was ignored and smoking was assessed on the basis of self-report alone, only the risk reduction in never smokers came close to statistical significance.

In this cardiovascular patients cohort, nonsmoking and cessation strongly predicted event-free survival. A statistically significant benefit could be seen only when smoking status was assessed with cotinine validation. Remarkably, the hazard ratios were at least as favorable for former smokers who had quit after their acute events as for never smokers, and smoking cessation appeared to lead to a reduction or normalization of cardiovascular risk very rapidly. A recent authoritative pertinent Cochrane review concluded that "it is unlikely that further work exploring the magnitude and speed of effect of smoking cessation is needed" (4). The findings described here urge us to voice dissent with this point of

Table 1 Cox Regression Results: Multivariate Survival Analysis for Fatal or Nonfatal Secondary Cardiovascular Disease Events, With Smoking Status Defined by Different Sources of Information

Smoking Status Definition	n (Events)	HR (95% CI)*	HR (95% CI)†
1. Cotinine at rehabilitation discharge (ng/ml)			
≥15	154 (30)	1.00 (reference)	1.00 (reference)
<15	908 (124)	0.57 (0.38–0.86)	0.52 (0.35–0.79)
2. Further differentiating abstainers according to self-report			
Continuing smoking (≥15 ng/ml)	154 (30)	1.00 (reference)	1.00 (reference)
Quit after acute event (<15 ng/ml)	169 (15)	0.45 (0.24–0.85)	0.38 (0.20–0.73)
Formerly smoking (<15 ng/ml)	423 (71)	0.69 (0.45–1.08)	0.62 (0.40–0.97)
Never smoking (<15 ng/ml)	316 (38)	0.47 (0.29–0.78)	0.47 (0.28–0.78)
3. Like definition 2, but restricted to subjects whose smoking status did not change during follow-up‡			
Continuing smoking (≥15 ng/ml)	98 (24)	1.00 (reference)	1.00 (reference)
Quit after acute event (<15 ng/ml)	101 (6)	0.22 (0.09–0.53)	0.17 (0.06–0.44)
Formerly smoking (<15 ng/ml)	361 (58)	0.46 (0.28–0.75)	0.42 (0.25–0.70)
Never smoking (<15 ng/ml)	287 (34)	0.33 (0.19–0.57)	0.32 (0.18–0.55)
4. Self-report at baseline			
Continuing smoking	53 (10)	1.00 (reference)	1.00 (reference)
Quit after acute event	204 (27)	0.68 (0.33–1.41)	0.75 (0.35–1.60)
Formerly smoking	468 (78)	0.63 (0.32–1.24)	0.68 (0.33–1.37)
Never smoking	337 (39)	0.41 (0.20–0.84)	0.48 (0.23–1.02)

Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). *Adjusted for sex and age. †Adjusted additionally for prevalent diabetes, triglycerides, total and low-density lipoprotein cholesterol, and angiotensin-converting enzyme medication at discharge. ‡Changes in smoking status as assessed by cotinine measurements at years 1 and 3 follow-up; also see text for clarification.

CI = confidence interval; HR = hazard ratio.

view. Future studies need to carefully account for the various types of misclassification to better understand the benefits of smoking cessation, as such knowledge is necessary for fully informing smoking patients about the impact their own behavioral choices have on their prognoses.

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